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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 01/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/080,713	COLMAN ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *62-67,70-73 and 75-133* is/are pending in the application.

4a) Of the above claim(s) *91-97 and 128-130* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *62-67,70-73,75-90,98-127 and 131-133* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' Amendment, filed 10/20/04, has been entered. Claims 62-67, 70-73, 75-90 have been amended. Claims 91-133 have been added.

Election/Restrictions

Newly submitted claims 91-97 and 128-130 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the claims are directed to transgenic animals produced by the claimed methods. The originally examined method claims are related to the newly submitted claims (91-97 and 128-130) as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case, the transgenic animals that are instantly claimed can be produced by another and materially different process, for example, by the targeting of an endogenous locus in a mouse ES cell to produce a transgenic mouse.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 91-97 and 128-130

are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 62-67, 70-73, 75-133 are under pending. Claims 62-67, 70-73, 75-90, 98-127 and 131-133 are under current examination. Claims 91-97 and 128-130 are withdrawn as being directed to a non-elected invention.

Priority

Applicants' submission of certified copies of the UK Applications on 3/4/99 [9905033.8] and 7/20/99 [9917023.5] has been received and is found to be proper.

Information Disclosure Statement

Applicants' Supplemental IDS, filed 7/16/04, has been considered and made of record.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 62-67, 70-73, 75-90, 98-127 and 131-133 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such

a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are broadly directed to methods for producing a transgenic non-human animal by modifying the nuclear genome of a somatic cell ad an endogenous locus by a genetic targeting event; transferring the modified nuclear genome of said somatic cell to a recipient cell to produce a nuclear transfer (NT) unit, activating the NT unit thereby producing an animal embryo; transferring the embryo to a surrogate mother; and allowing the animal embryo to develop to term to produce a transgenic non-human animal. In further embodiments, the claims are directed to methods for producing transgenic offspring by breeding the resulting transgenic animal.

Applicants' argue that Applicants need only teach one method to carry out the claimed subject matter and point to Amgen, Inc. v. Hoescht Marion Roussel, Inc. and Transkaryotic Therapies (TKT), Inc. as an analogy to the instant case.

This is not found to be analogous to the instant situation. The basis of this case, as stated by Applicants is that Amgen described one method to produce EPO by cloning the EPO DNA sequence and then expressing the encoded polypeptide in a suitable host cell (in particular, Amgen used a CHO cell). TKT denied the infringement of the patents because Amgen had failed to enable the method of genetic modification used by TKT to achieve the production of EPO, namely using a regulatory sequence of DNA to switch on the endogenous EPO gene to produce EPO.

Thus, TKT argued that the process used to produce the EPO substantially differed from the method taught by the Amgen patent, which required a heterologous EPO-encoding sequence. The CAFC stated (and as is indicated by Applicants) that, "[W]here the method is immaterial to the claim, the enablement inquiry simply does not require the specification to describe technological developments concerning the method by which a patented composition is made that may arise after the patent application is filed." Further, Applicants specifically point to the statement that, "the law makes clear that the specification need only one mode of making and using the claimed composition." See p. 13, last ¶ of Applicants' Response and the decision of Amgen, supplied by Applicants. Applicants argue that thus, it follows that the prior rejections of record do not follow the reasoning behind the Amgen, Inc. v. Hoescht Marion Roussel, Inc.

This is not persuasive. The instant application is directed to *methods*, not compositions. Thus, if a method is immaterial to the claim then the Examiner agrees that the specification need not describe technology that does not exist at the time of filing. However, in the instant case, the claims are directed to methods, and the enablement provision must show that the application provide sufficient disclosure such that one of skill in the art could practice the invention without undue experimentation and relying upon the specification and the knowledge in the art. See p. 12, 2nd ¶ of Applicants' Response. Thus, it follows that the teachings relied upon in the specification and art must provide sufficient guidance for the

skilled artisan to practice the claimed invention without undue experimentation. This is not the instant case. As stated in the prior Office action, the state of the art of nuclear transfer is not found to be predictable without specific guidance provided by the specification. The breadth of the instant claims are not found to be predictable with regard to various factors (cited in the previous Office action, and to be specifically addressed here).

Applicants argue that the instant specification is enabled for the breadth of any somatic cell to be used as a donor cell in nuclear transfer. Applicants argue that because, in the parent case, the Examiner had previously rejected similar claims and then did not maintain the rejections, that Applicants believed the rejection to be successfully overcome. See p. 15, 2nd full ¶ of the Response. Nevertheless, Applicants argue that they only have the burden of establishing that they have provided one clear method of enablement for the claims at issue. Applicants argue that they have done this, specifically that they have taught how to use serum starvation to create G_0 donor cells. Further, Applicants argue that other methods of accomplishing reprogramming, such as chemical treatments, growth inhibition or manipulation of gene expression, were well-known in the art at the time of filing of the instant application. Applicants point to specific references to support this. See p. 15-16 of the Response.

This is not persuasive. Firstly, it is reiterated that the claims are directed to methods of nuclear transfer, not products. Thus, the methods, as instantly claimed

must be enabled. The case law, as cited by Applicants, does not state that Applicants need only provide one clear method for enablement with regard to method claims because it is directed to product claims. The cited art of record (see p. 16 of the Response) has been considered but not found to be persuasive because the cited art fails to provide specific teachings to overcome the unpredictability in the state of the art of nuclear transfer with regard to the specific donor cell to be used. This unpredictability is further compounded by specific requirements for specific species, because it is art-recognized that not all donor cells can be used in all animal species to produce a live animal, which is required by the claims. The Examiner addresses this point in the prior Office action citing Fulka *et al.* (see p. 4-5 of the prior Office action). This is additionally supported by Oback (**Cloning & Stem Cells**, 4(2):147-168 (2002)) who review the state of the art for donor cells used in cloning and state, "Currently, we do not know what makes a good donor cell. In mammals, more than 200 distinct cell types are plainly distinguishable by morphology and more will probably be discovered when better molecular markers become available. Less than 5% of these have been tested as nuclear donors, and they all support development to blastocysts; however, many repeatedly failed to generate viable offspring." See p. 147, 2nd column, 1st ¶. Oback further supports the lack of teachings provided in the art with regard to donor cells that predictably result in live offspring by showing that in different animal species, different somatic donor cells have been tested with varying results. For example, Wakayama and

Yanagimachi tested eight cell types in NT methodology in mice, and found that live offspring were obtained from fibroblast, undefined fetal gonadal and cumulus cells. Further, Kato tested somatic donor cells in cattle and found that all supported development to blastocysts but live offspring were obtained from cumulus, oviduct, skin and liver cells. See pp. 155-156 of Oback. Further, Oback teaches that deciding which cell to use as a donor cell in NT methods is not clear because the cells that have worked in certain species are not the same cells that work in other species, and that they are often dissimilar in their cell cycle stage and their cloning competence. Oback provide a summary of cloning efficiencies from various somatic donor cells (see Table 1). It is noted that different cell types provide different cloning efficiencies with regard to different animal species. Thus, when taken with the specification's lack of teachings or guidance to enable the full breadth of the claimed invention (of any somatic cell donor) and the state of the art's clear teaching of the unpredictability of using any somatic cell as a donor in NT methodology, and the unpredictability amongst species of animals in using different somatic cells, it is maintained that the claims are not enabled. Note further that each application is examined on its own merits. Thus, upon consideration of the instant application, this rejection is found to be proper.

Applicants argue that, with regard to the gene targeting of somatic cells, Applicants argue that the present invention provides working examples from three different species (*i.e.*, ovine, porcine and bovine) and two different cell types

(fibroblasts and epithelial cells) which clearly establish the breadth of the method. See pp. 16-17, bridging ¶ of the Response. Applicants further argue that they need not teach only highly efficient methods to accomplish the invention, but that the patent must teach at least one mode to carry out the claimed invention, and that that the instant invention provides the fundamental advance that homologous recombination in somatic cells and nuclear transfer methods can be successfully combined. See p. 17, 2nd ¶ of the Response.

This is not found to be persuasive. It is reiterated that the instant specification fails to provide teachings or guidance with regard to using any somatic cell for gene targeting, and the state of the art clearly teaches that the gene targeting of somatic cells is unpredictable in nuclear transfer due to the premature senescence that often occurs and the low cloning efficiency associated with this senescence. See prior Office action, page 6 and Thomson, cited in the prior Office action. Although Applicants have provided working examples from three different species using fibroblasts and mammary epithelial cells, the breadth of the claims are not enabled because each recited step must be enabled to enable the invention. The state of the art of donor cell technology is such that it would not be predictable that any somatic cell could successfully be modified, and further, that a resulting genetically modified somatic cell could then be successfully used in NT methodology to produce a live transgenic animal. This is supported by Oback, who clearly teach that not only is the donor cell used in NT methodology unpredictable, but that it is

particularly unpredictable in producing viable clones. Thus, specific guidance must be provided by the specification to enable the claimed invention. Although Applicants have provided specific working examples with regard to gene targeting in ovine fetal fibroblasts (see Examples 1 and 3), porcine fetal fibroblasts (Example 6) and primary bovine fetal fibroblasts (example 7) and ovine mammary epithelial cells (example 5), the specification fails to provide sufficient guidance to show that these gene targeted cells result in live born animals in a predictable manner. The specification teaches the generations of live born lambs using primary ovine fibroblasts (examples 1 and 3) but do not provide any working examples with regard to the other recited cell types from other species. It is reiterated that the breadth of the claims is directed to any somatic cell type which must first be able to be genetically modified at a specific endogenous locus, and then the resulting transgenic somatic cell must then be used in a NT method to produce a non-human transgenic animal. The state of the art clearly shows that these steps are unpredictable with regard to the specific somatic cell that is to be used, and the further development of the NT unit to form an embryo and then develop to term. Note further that specific embodiments of the claimed invention are directed to specific animals (such as sheep, cow, bull, goat, pig, horse, camel, rabbit or rodent, see, for example, claim 63). This is not found to be enabling for the reasons cited previously and specifically because the specification fails to provide specific teachings with regard to the generation of these transgenic animals, for example,

the particular somatic cell to be used as a donor cell. The state of the art clearly teaches that the donor cells to be used in somatic NT methods are neither predictable nor routine for different species (see above), and the specification fails to overcome this art-recognized unpredictability. Furthermore, specific embodiments of the claims are directed to producing transgenic offspring from the resulting transgenic animals. The specification fails to provide an enabling disclosure for these embodiments because there are no specific teachings which overcome the art's unpredictability with regard to the generation of viable offspring. Applicants' argument that they need only provide one mode to carry out the claimed invention is not persuasive. The mode requirement is not addressed in an enablement rejection as it is the third requirement under 112, 1st paragraph (see MPEP §2165).

Note further that Applicants' support the unpredictability in the state of the art with regard to homologous recombination in somatic cells. In Applicants' response, it is stated, "One of ordinary skill therefore would have no reason to predict that the nuclear genome of a somatic cell could be modified at an endogenous locus by a genetic targeting event and that the nucleus of the genetically modified somatic cell could be used to accomplish successful nuclear transfer, prior to the work of the presnt inventors." See p. 23 of the Response. Further Applicants state that, "The ultimate production of live animals is a stringent test for donor cell normality, and success could not have been said to be obvious or expected." See p. 23 1st ¶ of the Response. Thus, it is clear by

Applicants' own admission that the art of NT, and particularly the use of somatic cells for specific gene targeting by homologous recombination and the subsequent nuclear transfer methods, is unpredictable, and further, that the generation of live animals produced from these nuclear transfer methods is unpredictable.

Applicants argue that the breadth of the claims recite methods of NT utilizing recipient cells, which include, but are not limited to, oocytes. Other types of recipient cells that can be used are, for example, zygotes and two-celled embryos. Applicants argue that the claimed invention does not rely upon any special method of NT and that the present invention is not directed to NT and does not provide any advance in the NT art, *per se*. Applicants argue that the invention is a fundamental achievement of the combination of gene targeting and NT, and thus, any method of NT may be used in accordance with the methods of the claimed invention. Applicants argue that the three types of oocytes recited in the prior Office action (metaphase I, II and telophase) can be used in NT, but that other types of oocytes may be discovered in the future. Applicants argue that because the invention is not NT, Applicants should not be limited to a specific method where the public can produce genetically modified animal, wherein the gene is modified by a genetic targeting event. Further, Applicants argue that they are not required to describe in the specification every conceivable and possible future embodiment of the invention and that the specification's teaching of NT to an oocyte is sufficient to enablement the claimed invention because the type of oocyte is not relevant, and

that any oocyte can be used in NT, which is known to one skilled in the art of cloning, can be used. Applicants argue that they fulfill the burden to providing at least one way to carry out the claimed method. See pp. 17-18 of the Response.

This is not persuasive. Firstly, Applicants' assertion that "other oocytes may be discovered in the future" is not germane to this enablement rejection. The claimed invention must be enabled at the time of filing. MPEP §2164 states the following:

> "Any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, **when filed**, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention." (Emphasis added).

The instantly claimed invention is not found to be enabling for the breadth of any recipient cell to be used in an NT method to produce a transgenic animal. The working examples provided by the specification show MII oocytes. The breadth of the claim is to any recipient cell (including cells other than oocytes). Although it is recognized that particular cell types (including zygotes and 2-celled embryos) are capable of being used in NT methods to produce live born animals, the art is certainly not predictable with regard to using any recipient cell. Furthermore, the claims recite any recipient cell, however, the specification and the art support using enucleated recipient cells. Clearly, if the recipient cells are not enucleate, the resulting embryo would be tetraploid. Applicants' arguments that the invention is not nuclear transfer *per se*, and that therefore, should not be limited to a specific

method to produce the transgenic animals is not found to be persuasive. The claims as broadly are not enabled for reasons set forth in this Office action and the prior Office action. Although Applicants are not required to describe every conceivable and possible future embodiment of the invention, the claimed invention must be described by the disclosure such as to enable one of skill in the art to make and use the claimed invention without undue experimentation. Thus, the breadth of the claims are not found to be enabling with regard to 1) the type of somatic cell to be used as a donor cell and 2) the recipient cell used. Note that, as stated previously, that for the claimed invention to be enabling, each method step must be enabling. The requirement for enablement is not that Applicants provide at least one way to carry out the method.

Applicants' arguments, with regard to the requirement for activation of the NT unit is found to be persuasive in view of Applicants' amendment to the claims reciting this activation step. See pp. 18-19 of the Response.

Applicants argue that, with regard to the surrogate mother requirement, Applicants have amended the claims to provide this step but disagree with regard to the Examiner's assertion that the embryo and surrogate mother be of the same species. Applicants provide examples to show that various combinations of species can successfully carry an embryo of another species. See p. 19 of the Response. Applicants argue that thus, the successful cloning of one species that is gestated in the womb of another species has been accomplished and provide post-filing art to

show that Lanza *et al.* reported the birth of a cloned bull guar brought successfully to term by a domestic cow as a surrogate mother. Applicants argue that, as affirmed by the CAFC in the Amgen case, future developments in the art can be encompassed by claims of an earlier filed patent application, and thus Applicants should not be limited to claims wherein the animal cloned is gestated in the womb of an animal of the same species. See pp. 19-20 of the Response.

This is not found to be persuasive. Applicants have misapplied the Amgen case law, as the instant claims are directed to methods of nuclear transfer (not products, as in the Amgen case) and that Applicants' instantly claimed invention must be enabled at the time of filing (see above, additionally). Thus future developments with regard to enablement are not considered germane to the instant invention. With regard to the species-specific requirement, it is noted that there is art-recognized discord between the term "species" in taxonomy versus the art which Applicants cite (for example, Lanza *et al.*). It is recognized that what is taxonomically termed genus, is what the Examiner (and the art supports) recognizes as a species of animal. For example, although Prezewalski horse and Grant's zebras can be gestated in the womb of a domestic mare, where both are found in the same taxonomic genus (*i.e.*, Equus), it is evident that a horse embryo (taxonomic genus *Equus*) cannot be gestated in the womb of a cat (taxonomic genus *Felis*). The breadth of Applicants' claims encompass both described scenarios. However, if Applicants wish to clearly correct on the record that the term "species"

is meant to consist only of those animals within a taxonomic genus which are able to carry the resulting NT unit to term, Applicants are invited to do so.

Applicants' arguments with regard to cloning of humans is rendered moot in view of Applicants' amendments to the claims to recite "non-human". See p. 20, 1st ¶ of the Response.

Applicants argue that with regard to the prior rejection that the genetic targeting event result in a gene targeted cell:randomly targeted cell clone ratio of 1:100, and that promoter directs abundant expression in fibroblast cells is now rendered moot because Applicants have cancelled these claims. See p. 20, ¶ (vii) of the Response. This is not persuasive the prior rejection of record is maintained. Applicants' newly added claims recite this limitation (see claims 101, 105, for example). It is reiterated that the specification fails to provide specific guidance with regard to the breadth of the claims. See p. 11 of the prior Office action. The general term of "abundant expression" is insufficient guidance for the artisan to know what particular gene meets this definition. Furthermore, there is no guidance as to what locus, other than the exemplified collagen locus, which would provide the claimed 1:100 gene targeted cell:randomly targeted cell clone ratio. It is further maintained that the specification fails to provide guidance as to other means of genetic targeting, other than homologous recombination. The working example provided by the instant specification is by preparation of a vector for homologous recombination, and without further teachings with regard to the characteristics

that of abundant expression of a particular endogenous gene locus, or what would make a gene targeting event result in a gene target cell:randomly targeted cell clone ratio of equal to or greater than 1:100, the specification fails to enable the breadth of the claims.

Applicants argue that the instant application is directed to the generation of transgenic animals but concerns the genotype not the phenotype, and that there is no requirement in the claims that the genetic modification result in an altered phenotype in the transgenic animals. Thus, Applicants argue that the pending claims are directed only to methods to produce animals which bear a transgene at a specified location within the genome of the animal. See p. 20, ¶ (viii) of the Response.

This is not persuasive. The resulting transgenic animal's phenotype is a direct result of the genotypic alteration. If there is no apparent phenotype present in the resulting animal, one of skill would not know how to use the transgenic animal. Thus, animals without a phenotype would not be discernable from wild-type animals, and these animals would not have an enabled use. Thus, it is maintained that the specification fails to provide specific guidance for the breadth of producing any transgenic non-human animal whose genome comprises a modification at an endogenous locus by a gene targeting event, and thus, it would have required undue experimentation to predict the results achieved in any one

hose animal comprising and expressing a particular transgene, the levels of the transgene product, the consequences of that product, and the resulting phenotype.

Note that newly added claims are directed to the modification of specific genes, for example, claims 123-124 are directed to inactivation of the endogenous alpha 1-3 galactosyltransferase gene and claim 125 is directed to the modification of the endogenous immunoglobulin gene locus. These claims are not enabled for the reasons stated previously. More specifically, the claims are not enabling because although the specification has provided a specific teaching for the generation of knockout alpha 1-3 galactosyltransferase primary porcine fetal fibroblasts (see Example 6), it is maintained that there is no expectation of success, with regard to the breadth of the claims, that it would be feasible to knockout this gene in any particular somatic cell to use the resulting cell in a nuclear transfer method with any recipient cell and then transferring the resulting NT unit to a surrogate mother to produce a non-human transgenic animal. The state of the art has clearly shown that each of these steps has a specific unpredictability associated with it, and that, absent any particular teachings provided by the specification, it would have required undue experimentation for one of skill in the art to carry out the claimed methods.

Accordingly, for the reasons cited above, it would have required undue experimentation for the skilled artisan to carry out the claimed methods without an a predictable degree of success to implement the invention as claimed.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The prior rejections of claim 62 and its dependent claims and claim 90 are withdrawn in view of Applicants' amendments to the claims.

Claims 90, 97-127 and 133 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 90 recites the limitation "the nuclear transfer unit" in part (c) of the claim. There is insufficient antecedent basis for this limitation in the claim. Claims 97-127 depend from claim 90.

The term "abundant" in claims 105 is a relative term which renders the claims indefinite. The term "abundant" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is unclear how much expression would constitute abundant expression, as such the claims are indefinite. The terms "abundant" is relative terms in the absence of some standard of comparison. Thus, it is unclear what constitutes the metes and bounds of this term.

Claim 133 is unclear. The claim recites that the animal embryo is allowed to mature "in a manner that accomplishes breeding". It is unclear how an embryo matures such that it can accomplish breeding. Appropriate correction is required.

Claim 133 recites the limitation "the nuclear transfer unit" in part (c) of the claim. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The prior rejection of claims 62-75, 82-87 and 90 under 35 U.S.C. 103(a) as being unpatentable over Schnieke *et al.* in view of Stacey *et al.* [Ref. AT 28] and Stacey *et al.* is withdrawn in view of Applicants' arguments, in particular, Applicants statement that in view of the closest prior art cited by the Examiner (Schnieke, Stacey and Stacey), "One of ordinary skill therefore would have no reason to predict that the nuclear genome of a somatic cell could be modified at an endogenous locus by a genetic targeting event and that the nucleus of the genetically modified somatic cell could be used to accomplish successful nuclear

transfer, prior to the work of the present inventors." See p. 23 of the Response, 2nd ¶.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Amy Nelson, Acting SPE of Art Unit 1632, at (571) 272-0804. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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